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Nucleation Time in Stochastic Becker-Döring Model

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Amyloid diseases and Becker-Döring model

Numerical results

Coarse-graining

Large deviations

Outline

Amyloid diseases and Becker-Döring model

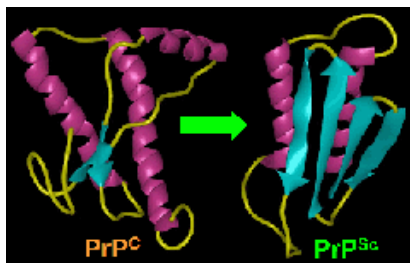
Numerical results

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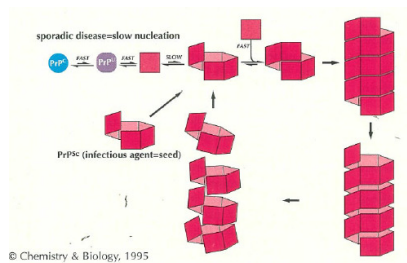
Large deviations

Protein accumulation in amyloid by nucleation-polymerization

Misfolding



Prusiner model for prion

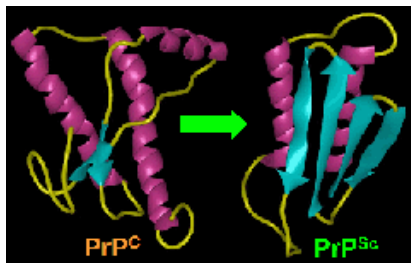


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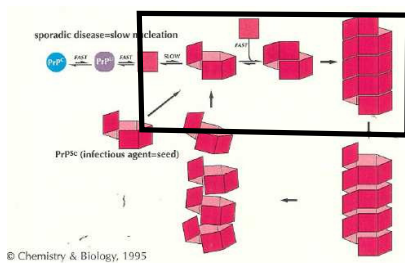
Mechanism of Prion Propagation: Amyloid Growth Occurs by Monomer Addition

Protein accumulation in amyloid by nucleation-polymerization

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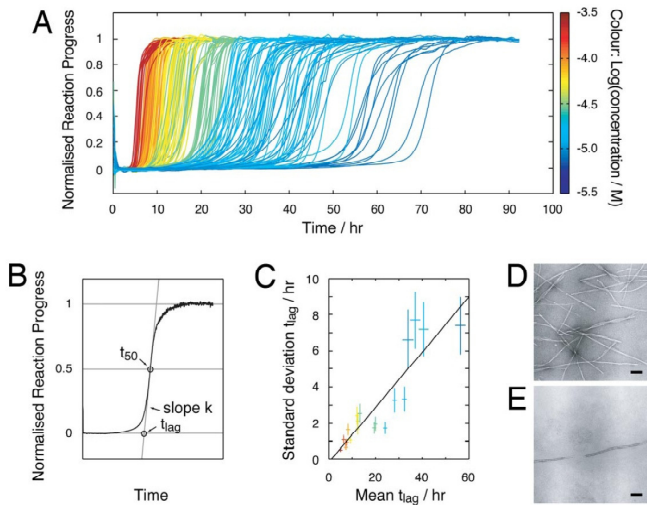


Prusiner model for prion



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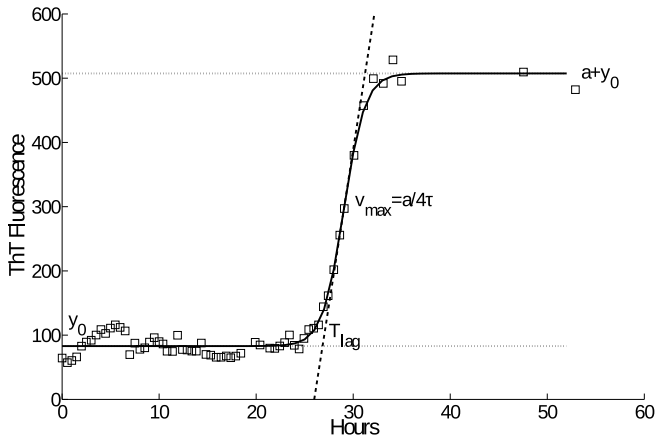
Mechanism of Prion Propagation:
 Amyloid Growth Occurs by **Monomer Addition**

Times series of *in-vitro* spontaneous polymerization

Xue et al. PNAS (2008)

Eugene et al. hal-01205549 (2015)

Quantification of experiment

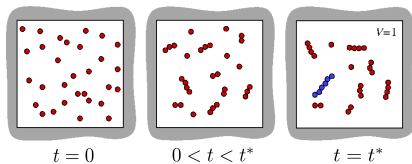
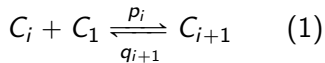


ThT fluorescence \approx Number of polymerized protein

[Courtesy of J.P. Liautard]

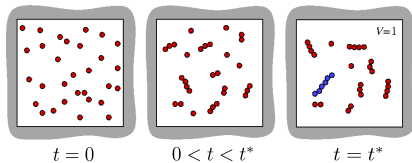
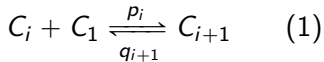
Becker-Döring model

Reversible one-step aggregation



Becker-Döring model

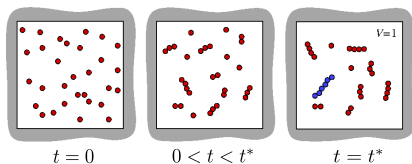
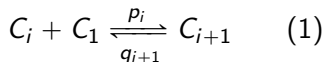
Reversible one-step aggregation



- Purely dynamic model (law of mass-action) : no space, no polymer structure.

Becker-Döring model

Reversible one-step aggregation

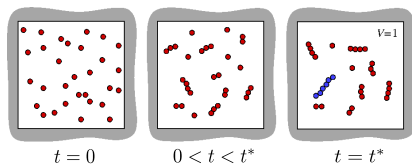
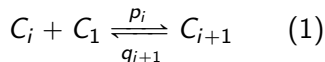


- ▶ Indirect interaction between polymer C_i , $i \geq 2$ via the available number of monomers C_1 .

$$C_1(t) + \sum_{i \geq 2} i C_i(t) = \text{constant} := M \quad (2)$$

Becker-Döring model

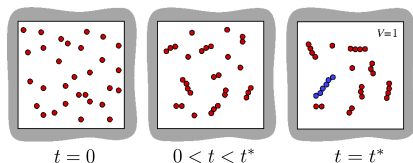
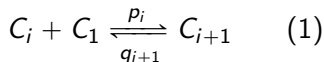
Reversible one-step aggregation



- ▶ In spontaneous polymerization experiment,
 - ▶ Initial condition given by $C_i(t = 0) = 0 \forall i \geq 2$.
 - ▶ Measured variable : $\sum_{i \geq N} i C_i$ (N is an unknown parameter)

Becker-Döring model

Reversible one-step aggregation



- ▶ The (observed) nucleation time is given by

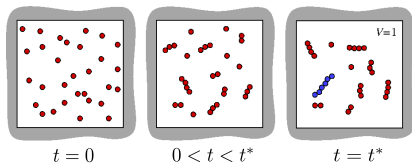
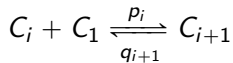
$$\inf\{t \geq 0 : \sum_{i \geq N} i C_i(t) \geq \rho M \mid C_i(t=0) = M \delta_{i=1}\}.$$

Another quantity of interest is the following **First Passage Time**,

$$\inf\{t \geq 0 : C_N(t) \geq \rho \mid C_i(t=0) = M \delta_{i=1}\}.$$

Becker-Döring model

Reversible one-step aggregation



- ▶ What are the dependencies of the nucleation time with respect to the model parameters?

total mass : M ; nucleus size : N

aggregation rates : $p_i, i \geq 1$ fragmentation rates : $q_i, i \geq 2$

- ▶ What is the nucleation time for very large initial quantity M and nucleus size N ?
- ▶ In experiment, $M \approx 10^{10} - 10^{15}$,
Size of (observed) polymers $\approx 10^3 - 10^6$, $N = ?$.

Deterministic BD model and Classical Nucleation Theory

$$\left\{ \begin{array}{l} \frac{dc_i}{dt} = J_{i-1} - J_i, i \geq 2, \\ J_i = p_i c_1 c_i - q_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} = -J_1 - \sum_{i=1}^{\infty} J_i. \end{array} \right.$$

Equilibrium is given by $J_i \equiv J = 0$, which implies

$$c_i = Q_i c_1^i, \quad Q_i = \frac{p_1 p_2 \cdots p_{i-1}}{q_2 q_3 \cdots q_i}$$

The mass at equilibrium is given by

$$\rho(c_1) = \sum_{i \geq 1} i Q_i c_1^i$$

If this series has a finite radius of convergence, z_s , then there is a critical mass

$$\rho_s = \sum_{i \geq 1} i Q_i z_s^i$$

Deterministic BD model and Classical Nucleation Theory

[Ball, Carr, Penrose,
CMP (1986)]

$$\begin{cases} \frac{dc_i}{dt} = J_{i-1} - J_i, i \geq 2, \\ J_i = p_i c_1 c_i - q_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} = -J_1 - \sum_{i=1}^{\infty} J_i. \end{cases}$$

If $M \leq \rho_s$, then (with strong convergence)

$$\lim_{t \rightarrow \infty} c_i(t) = Q_i z^i, \quad \rho(z) = M$$

If $M > \rho_s$, then (with weak convergence)

$$\lim_{t \rightarrow \infty} c_i(t) = Q_i z_s^i, \quad M - \rho(z_s) = \text{"loss of mass"}$$

As $M \searrow \rho_s$, there is a solution for which $J_i \approx J^*$ is exponentially small, and

- ▶ (for finite t) $c_i(t) - c_i(0)$ is exponentially small
- ▶ $\lim_{t \rightarrow \infty} c_i(t) - c_i(0)$ is not exponentially small

Deterministic BD model – Some remarks

- ▶ For constant or linear kinetic rates p_i, q_i , one can reduce the system to 1 or 2 ODEs on

$$\sum_{i \geq 1} c_i, \quad \sum_{i \geq 1} i c_i.$$

- ▶ Based on scaling arguments, one can show that for $q_i = 0$ (irreversible nucleation),

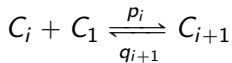
$$\inf\{t \geq 0 : c_N(t) \geq \rho M \mid c_i(t=0) = M\delta_{i=1}\} \simeq \frac{1}{M}.$$

while for “ $q_i \rightarrow \infty$ ” (pre-equilibrium nucleation),

$$\inf\{t \geq 0 : c_N(t) \geq \rho M \mid c_i(t=0) = M\delta_{i=1}\} \simeq \frac{1}{M^N}.$$

Stochastic Becker-Döring model

Reversible one-step aggregation

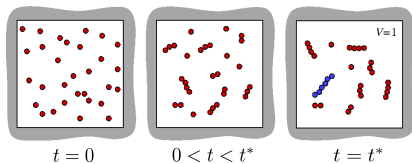


We define a continuous time Markov Chain on

$$\{(C_i)_{i \geq 1} : C_i \in \mathbb{N}, \sum_{i \geq 1} i C_i = M\}$$

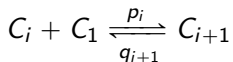
Transitions are given by

$$\mathcal{P} \left\{ \begin{array}{l} C_1(t+dt) = C_1(t) - 1 \\ C_i(t+dt) = C_i(t) - 1 \\ C_{i+1}(t+dt) = C_{i+1}(t) + 1 \end{array} \right\} = p_i C_1(t) C_i(t) dt + o(dt)$$



Stochastic Becker-Döring model

Reversible one-step aggregation

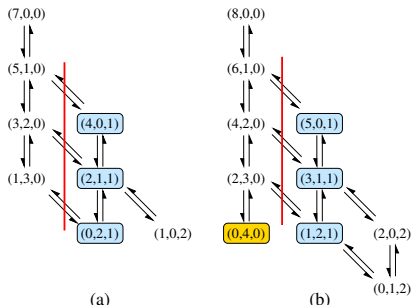


We define a continuous time
Markov Chain on

$$\{(C_i)_{i \geq 1} : C_i \in \mathbb{N}, \sum_{i \geq 1} i C_i = M\}$$

We are interested in

$$\inf\{t \geq 0 : C_N(t) \geq 1 \mid C_i(t=0) = M\delta_{i=1}\}.$$



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- ▶ Law of large numbers as $M \rightarrow \infty$ [Jeon. CMP (1998)]
- ▶ Any macroscopic quantity like.

$$\inf\{t \geq 0 : \sum_{i \geq N} i C_i(t) \geq \rho M$$

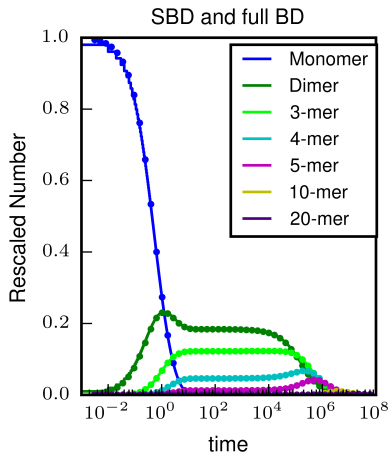
$$| C_i(t=0) = M \delta_{i=1}\}.$$

converges (if reachable) to a finite deterministic value as $M \rightarrow \infty$.

- ▶ This may not be true for microscopic quantity, for instance.

$$\inf\{t \geq 0 : C_N(t) \geq 1$$

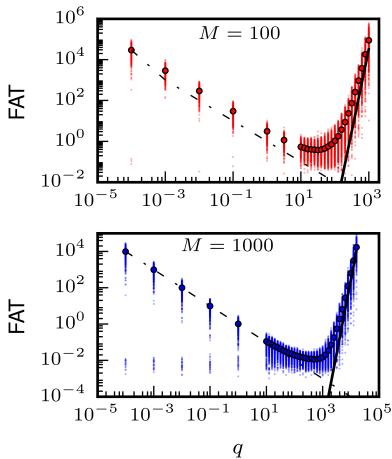
$$| C_i(t=0) = M \delta_{i=1}\}.$$



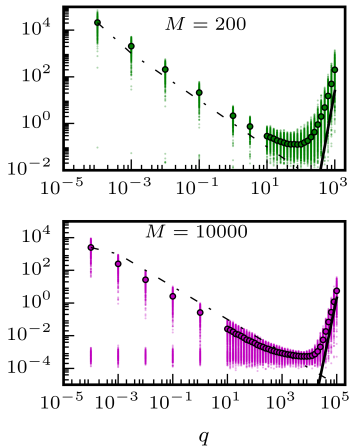
[Y., D'Orsogna, Chou JCP (2012)]

[Y., Bernard, Hingant, Pujon-Menjouet JCP (2016)]

- ▶ Non-monotonous w.r.t reaction rate



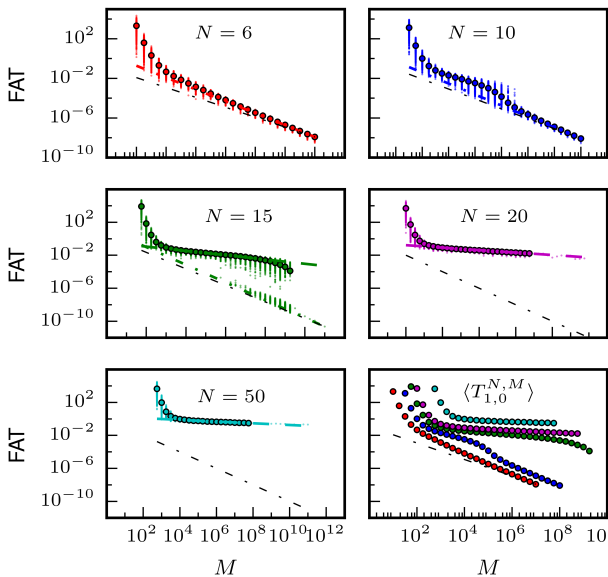
- ▶ Bimodal for 'small' fragmentation rate



$N=10$, $p_1 = 0.5$, $p_k = 1$ and $q_k \equiv q$ for $k \geq 2$.

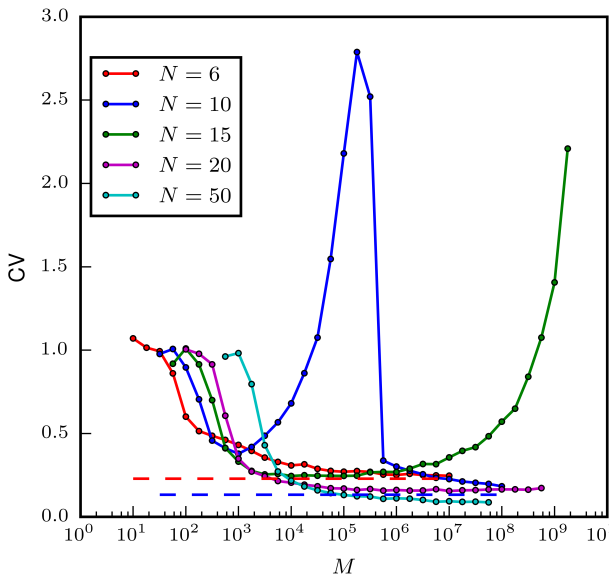
- 'Weak' dependency w.r.t. total monomer number M

$p_1 = 0.5$, $p_k = 1$
and $q_k \equiv 100$ for $k \geq 2$.



- ▶ Normalized standard deviation non-monotonous.
- ▶ Normalized standard deviation non-zero pour $M \rightarrow \infty$.

$p_1 = 0.5$, $p_k = 1$
and $q_k \equiv 100$ for
 $k \geq 2$.



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When $N \rightarrow \infty$?

We start from a rescaled model ($\varepsilon = 1/N$, $\varepsilon^2 = 1/M$)

$$\begin{cases} \frac{dc_i^\varepsilon}{dt} = \frac{1}{\varepsilon} [J_{i-1}^\varepsilon - J_i^\varepsilon], & i \geq 2, \\ m^\varepsilon = c_1^\varepsilon(t) + \varepsilon^2 \sum_{i \geq 2} ic_i^\varepsilon(t). \end{cases}$$

With $f^\varepsilon(t, x) = \sum_{i \geq 2} c_i^\varepsilon(t) \mathbf{1}_{[(i-1/2)\varepsilon, (i+1/2)\varepsilon)}(x)$,

Scaling idea : **excess of monomer**

$$c_1^\varepsilon(t) = \varepsilon^2 c_1(t),$$

Compensated aggregation / fragmentation

$$p^\varepsilon(x) = \sum_{i \geq 2} (p_i / \varepsilon^2) \mathbf{1}_{[\varepsilon i, \varepsilon(i+1)]} \quad q^\varepsilon(x) = \sum_{i \geq 3} q_i \mathbf{1}_{[\varepsilon i, \varepsilon(i+1)]}$$

and **slow first step** :

$$p_1^\varepsilon = \frac{p_1}{\varepsilon^4},$$

When $N \rightarrow \infty$?

We start from a rescaled model ($\varepsilon = 1/N$, $\varepsilon^2 = 1/M$)

$$\begin{cases} \frac{dc_i^\varepsilon}{dt} = \frac{1}{\varepsilon} [J_{i-1}^\varepsilon - J_i^\varepsilon], & i \geq 2, \\ m^\varepsilon = c_1^\varepsilon(t) + \varepsilon^2 \sum_{i \geq 2} ic_i^\varepsilon(t). \end{cases}$$

With $f^\varepsilon(t, x) = \sum_{i \geq 2} c_i^\varepsilon(t) \mathbf{1}_{[(i-1/2)\varepsilon, (i+1/2)\varepsilon)}(x)$,

From the polymer point of view, we have accelerated fluxes, all of the same order :

$$\begin{array}{c} \xrightarrow[\frac{1}{\varepsilon} q_2^\varepsilon C_2^\varepsilon]{\frac{1}{\varepsilon} p_1^\varepsilon C_1^\varepsilon C_1^\varepsilon} C_2^\varepsilon \\ \\ C_{i-1}^\varepsilon \xrightarrow[\frac{1}{\varepsilon} q^\varepsilon(\varepsilon i) C_i^\varepsilon]{\frac{1}{\varepsilon} p^\varepsilon(\varepsilon(i-1)) C_1^\varepsilon C_{i-1}^\varepsilon} C_i^\varepsilon \xrightarrow[\frac{1}{\varepsilon} q^\varepsilon(\varepsilon(i+1)) C_{i+1}^\varepsilon]{\frac{1}{\varepsilon} p^\varepsilon(\varepsilon i) C_1^\varepsilon C_i^\varepsilon} C_{i+1}^\varepsilon \end{array}$$

When $N \rightarrow \infty$?

We start from a rescaled model ($\varepsilon = 1/N$, $\varepsilon^2 = 1/M$)

$$\begin{cases} \frac{dc_i^\varepsilon}{dt} = \frac{1}{\varepsilon} [J_{i-1}^\varepsilon - J_i^\varepsilon], & i \geq 2, \\ m^\varepsilon = c_1^\varepsilon(t) + \varepsilon^2 \sum_{i \geq 2} ic_i^\varepsilon(t). \end{cases}$$

With $f^\varepsilon(t, x) = \sum_{i \geq 2} c_i^\varepsilon(t) \mathbf{1}_{[(i-1/2)\varepsilon, (i+1/2)\varepsilon)}(x)$,

$$\begin{cases} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx = [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2^\varepsilon c_2^\varepsilon(t)] \left(\frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ + \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \\ m^\varepsilon = c_1^\varepsilon(t) + \int_0^{+\infty} x f^\varepsilon(t, x) dx. \end{cases}$$

where $\Delta_\varepsilon \varphi(x) = \frac{\varphi(x+\varepsilon) - \varphi(x)}{\varepsilon}$.

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx &= [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2 c_2^\varepsilon(t)] \left(\frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ &+ \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \end{aligned}$$

Theorem (Deschamps, Hingant, Y. (2016))

we have $f^\varepsilon \rightarrow f$ (weakly in $\mathcal{X} = \{\nu \in \mathcal{M}_b([0, \infty)) : \int x \nu(dx) < \infty\}$)
solution of

$$\frac{d}{dt} \int_0^{+\infty} f(t, x) \varphi(x) dx = \int_0^{+\infty} [p(x) c_1(t) - q(x)] \varphi'(x) f(t, x) dx,$$

and $c_1(t) + \int x f(t, x) = m$, for all $\varphi \in C_c(0, \infty)$.

This is the weak form of

$$\frac{\partial f}{\partial t} + \frac{\partial(J(x, t) f(t, x))}{\partial x} = 0, \quad J(x, t) = p(x) c_1(t) - q(x).$$

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx &= [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2 c_2^\varepsilon(t)] \left(\frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ &+ \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \end{aligned}$$

Theorem (Deschamps, Hingant, Y. (2016))

When $c_1(0) > \lim_{x \rightarrow 0} \frac{q(x)}{p(x)}$,

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f(t, x) \varphi(x) dx &= N(t) \varphi(0) \\ &+ \int_0^{+\infty} [p(x) c_1(t) - q(x)] \varphi'(x) f(t, x) dx, \end{aligned}$$

for all $\varphi \in C_b(0, \infty)$, which gives the boundary condition

$$\lim_{x \rightarrow 0} J(x, t) f(t, x) = N(t).$$

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx &= [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2 c_2^\varepsilon(t)] \left(\frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ + \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \end{aligned}$$

Theorem (Deschamps, Hingant, Y. (2016))

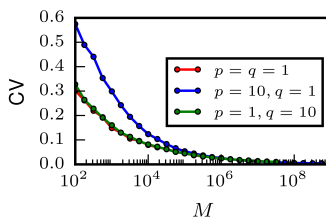
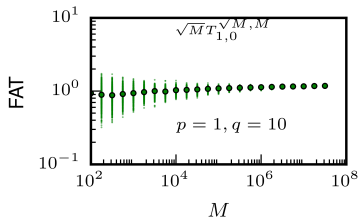
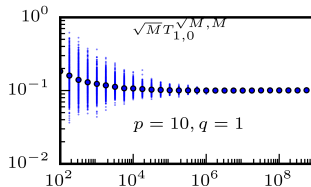
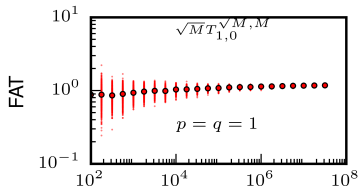
$N(t)$ is an explicit function of $c_1(t)$, and is given by a quasi steady-state approximation of $c_2^\varepsilon = f^\varepsilon(t, 2\varepsilon)$, given by the solution of

$$\begin{cases} 0 &= [J_{i-1}(c_1) - J_i(c_1)], \quad i \geq 2, \\ c_1(t) &= c_1. \end{cases}$$

When $c_1 > \lim_{x \rightarrow 0} \frac{q(x)}{p(x)}$, the solution of $J_i \equiv J \neq 0$ is linked to the loss of mass in the classical BD theory.

Large nucleus $N \sim \sqrt{M}$

- First case ($p(0)m > q(0)$) : Convergence towards a deterministic value.

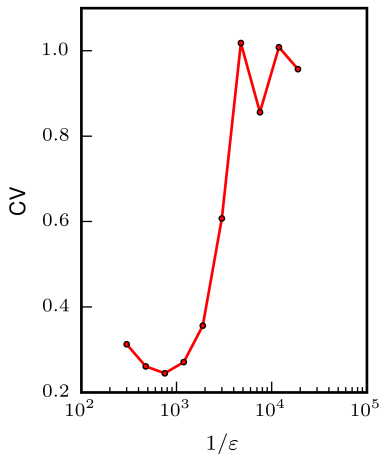
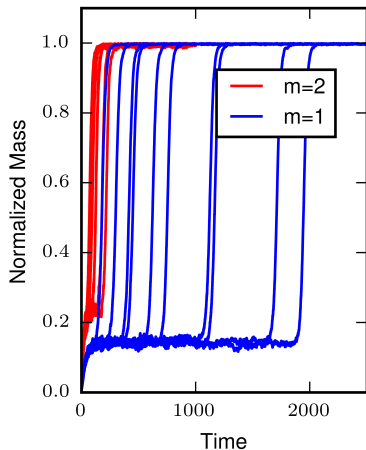


▶ case A

▶ case B

Large nucleus $N \sim \sqrt{M}$

- ▶ Second case ($p(0)M < q(0)$) : Exponentially large time and 'translated' trajectory.



Outline

Amyloid diseases and Becker-Döring model

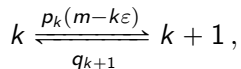
Numerical results

Coarse-graining

Large deviations

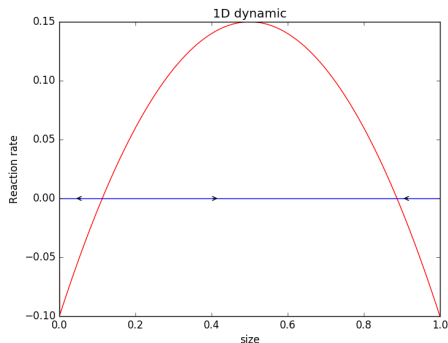
Quantifying the large deviation in toy model

A much simpler version of this model consider that a **single** aggregate may be formed at a time :



which converges (with time rescaling) to

$$\frac{dx}{dt} = p(x)(m-x) - q(x)$$



Quantifying the large deviation in toy model

A much simpler version of this model consider that a **single** aggregate may be formed at a time :

$$k \xrightleftharpoons[q_{k+1}]{p_k(m-k\varepsilon)} k+1,$$

which converges (with time rescaling) to

$$\frac{dx}{dt} = p(x)(m-x) - q(x)$$

- ▶ To leading order the stationary prob. density is

$$u^*(x) = C \frac{e^{-\frac{1}{\varepsilon} \int^x \log\left(\frac{q(y)}{p(y)(m-y)}\right) dy}}{\sqrt{p(x)(m-x)q(x)}}.$$

- ▶ MFPT is explicit and is exponentially large in ε
- ▶ The “rate” is exponentially small

Quantifying the large deviation in toy model

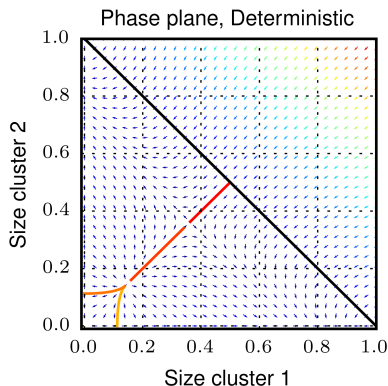
Can we perform similar calculations with n clusters?

$$(k_0, k_1) \xrightleftharpoons[q_{k_0+1}]{p_{k_0}(m-(k_0+k_1)\varepsilon)} (k_0 + 1, k_1),$$

$$(k_0, k_1) \xrightleftharpoons[q_{k_1+1}]{p_{k_1}(m-(k_0+k_1)\varepsilon)} (k_0, k_1 + 1),$$

which converges (with time rescaling) to

$$\begin{aligned} \frac{dx}{dt} &= p(x)(m-x-y) - q(x) \\ \frac{dy}{dt} &= p(y)(m-x-y) - q(y) \end{aligned}$$



Quantifying the large deviation in toy model

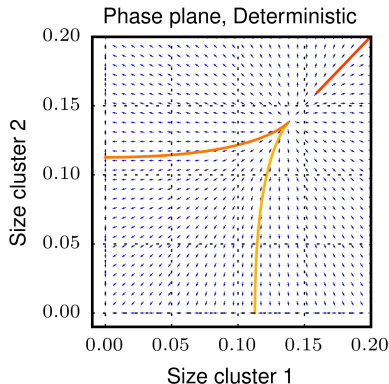
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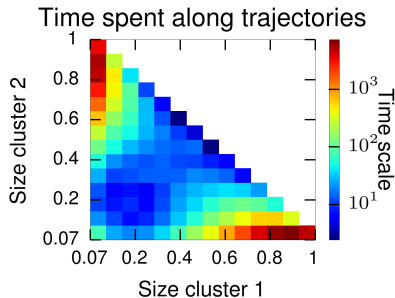
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$$\frac{dx}{dt} = p(x)(m - x - y) - q(x)$$

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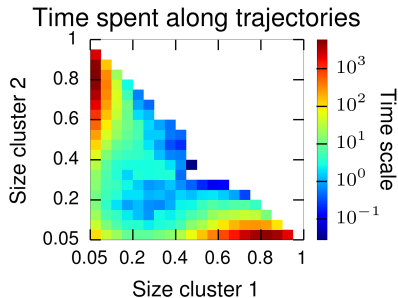
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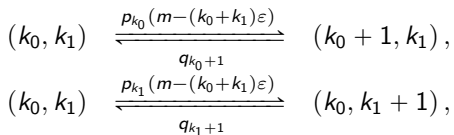
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Quantifying the large deviation in toy model

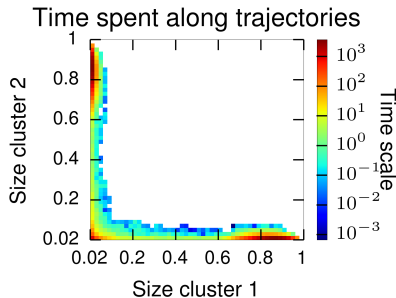
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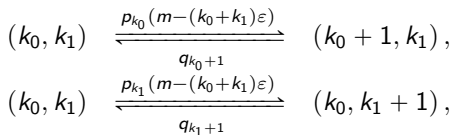
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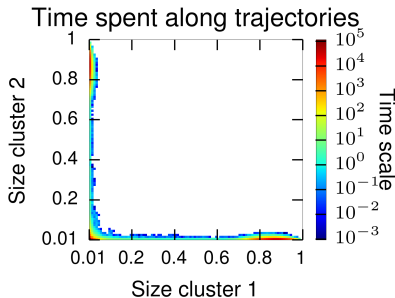
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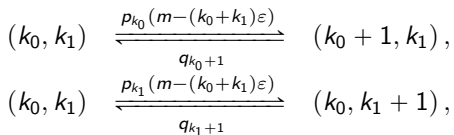
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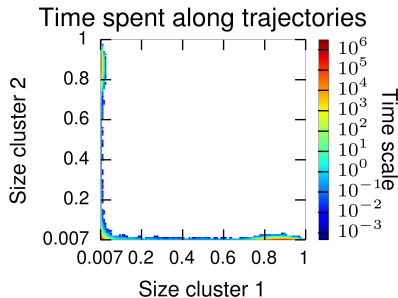
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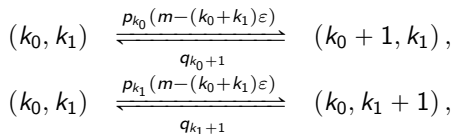
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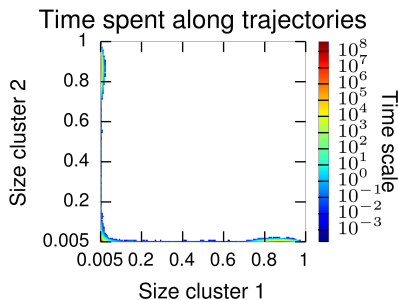
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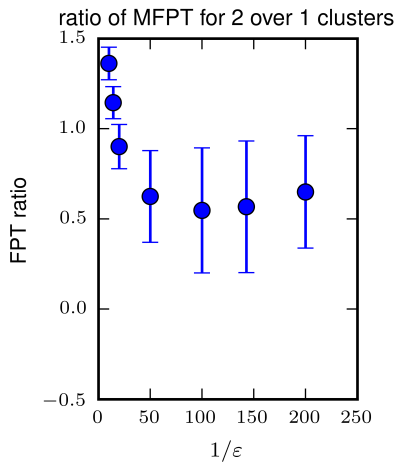
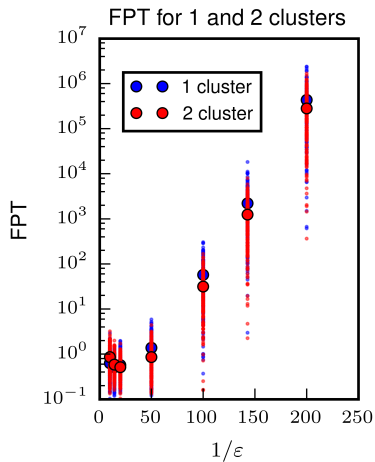


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Next :

- ▶ **Proving Large Deviation Principle for the full (S)BD**
- ▶ **Quantifying the MFPT**
- ▶ **Data fitting in spontaneous polymerization experiment**

Thanks for your attention !